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FINNEGAN HENDERSON FARABOW
GARRETT & DUNNER
FRANKLIN SQUARE BLDG SUITE 700
1300 I STREET N W
WASHINGTON, DC 200053315

EXAMINER

WHITE, EVERETT NMN

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BEFORE THE BOARD OF PATENT APPEALS
AND INTERFERENCES

Application Number: 09/101,672
Filing Date: October 23, 1998
Appellant(s): BARTLETT ET AL.

Paper No. 32

Date mailed

12/18/02

Carol P. Einaudi
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed July 17, 2002.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) *Related Appeals and Interferences*

A statement identifying the related appeals and interferences, which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) *Status of Claims*

The statement of the status of the claims contained in the brief is correct.

(4) *Status of Amendments After Final*

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) *Summary of Invention*

The summary of invention contained in the brief is correct.

(6) *Issues*

The appellant's statement of the issues in the brief is correct.

(7) *Grouping of Claims*

Appellant's brief includes a statement that claims 12, 15-17, 20-26, and 29 do not stand or fall together and provides reasons as set forth in 37 CFR 1.192(c)(7) and (c)(8).

(8) *Claims Appealed*

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) *Prior Art of Record*

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 12 and 15-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bartlett et al (US Patent No. 4,965,276).

Appellants claim a solid composition comprising a first component comprising 5-methyl-4"-trifluoromethyl-4-isoxazolecarboxanilide; a second component comprising the compound of the formula I, which is disclosed in Claim 12; a third component comprising a pharmaceutically tolerated excipient, wherein the first component has a concentration from about 2 to about 20 mg and the second component has a concentration from about 0.8% to about 15% of the first component.

The Bartlett et al patent discloses a pharmaceutical composition for use in the treatment of chronic Graft-versus-host diseases and autoimmune diseases such as systemic lupus erythematosus containing as the active ingredient at least one compound of the formula 1 or 2, compound 2 being present per se or in the form of a physiologically tolerable salt. The compound of formula 1 of the Bartlett et al patent embraces the first component of the composition of the instant claims because the first component having the name 5-methyl-4"-trifluoromethyl-4-isoxazolecarboxanilide represent the compound of formula 1 of the Bartlett et al patent. The compound of formula 2 of the Bartlett et al patent is analogous to formula I of the second component in the instant claims. The composition of the instant claims may differ from the compositions disclosed in the Bartlett et al patent by disclosing the first and second components together as one composition. It is not clearly stated in the Bartlett et al

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patent that compounds 1 and 2 have been combined together to form a composition. However, it is noted that the utility for the composition comprising compound formula 1 and 2 of the Bartlett et al patent are the same, that is, both compounds are used to treat chronic graft-versus-host diseases and autoimmune diseases such as systemic lupus erythematosus. Case law, *In re Kerkhoven*, 626 F2d 846, 205 USPQ 1069 (CCPA 1980), states that it is obvious to combine individual compositions taught to have the same utility to form a new composition for the very same purpose, which is what Appellants have done. The composition of the instant claims further disclose that the first component has a concentration from about 2 to about 20 mg and the second component has a concentration from about 0.8% to about 15% of the first component. However, the concentration of first and second components does not make the claims patentable over the Bartlett et al patent since case law states that synergism may be expected or unexpected (Synergism exhibited by a physical mixture of ingredients is a factor to be considered in determining the obviousness of the composition but it is not controlling since synergism may be expected or unexpected. *In re Hullmantel*, (CCPA 1963) 324 F2d 998, 139 USPQ 496; *Ethyl Corp. v. Ladd. Comr. Pats.* (DCDC 1963) 221 F Supp 751, 138 USPQ 663). Also, see column 6, lines 39-43, where Barlett et al discloses that the compositions can be prepared for oral and rectal administration, which embraces instant Claim 17. *In re Vaeck*, 947 F2d 488, 492, 20 USPQ 2d 1438, 1441 (Fed. Cir. 1991), states that for an invention to be obvious, two things must be found in the prior art: (1) the suggestion of the invention, and (2) the expectation of its success. In the instant case, both 1 and 2 are satisfied by the combination of the teachings of the Bartlett et al patent and the pertinent case law. Accordingly, it would have been obvious to one of ordinary skill in the art at the time of Appellants invention having the Bartlett et al patent before him to obtain the instantly claimed invention in view of the analogous structures of the compounds disclosed in the compositions and the resulting expectation of similar therapeutic properties.

Claims 20-26 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bartlett et al (US Patent No. 4,965,276).

Appellants claim a method of treating an immunological disease comprising administering to a patient in need of such treatment, a therapeutically effective amount of a solid composition comprising a first component comprising 5-methyl-4"-trifluoromethyl-4-isoxazolecarboxanilide; a second component comprising the compound of the formula I, which is disclosed in Claim 20, or a stereoisomeric form of the compound of formula I, or a physiologically tolerated salt of the compound of formula I; a third component comprising a pharmaceutically tolerated excipient, wherein the first component has a concentration from about 2 to about 20 mg and the second component has a concentration from about 0.8% to about 15% of the first component.

The Bartlett et al patent discloses a pharmaceutical composition for use in the treatment of chronic Graft-versus-host diseases and autoimmune diseases such as systemic lupus erythematosus containing as the active ingredient at least one compound of the formula 1 or 2, compound 2 being present per se or in the form of a physiologically tolerable salt. The compound of formula 1 of the Bartlett et al patent embraces the first component of the composition of the instant claims because the first component having the name 5-methyl-4"-trifluoromethyl-4-isoxazolecarboxanilide represent the compound of formula 1 of the Bartlett et al patent. The compound of formula 2 of the Bartlett et al patent is analogous to formula I of the second component in the instant claims. The method of the instant claims may differ from the method disclosed in the Bartlett et al patent by disclosing the first and second components together as one composition. It is not clearly stated in the Bartlett et al patent that compounds 1 and 2 have been combined together to form a composition. However, it is noted that the utility for the composition comprising compound formula 1 and 2 of the Bartlett et al patent are the same, that is, both compounds are used to treat chronic graft-versus-host diseases and autoimmune diseases such as systemic lupus erythematosus. *In re Kerkhoven*, 626 F2d 846, 205 USPQ 1069 (CCPA 1980) states that it is obvious to combine individual compositions taught to have the same utility to form a new composition for the very same purpose, which is what Appellants have done. The composition of the instant claims further disclose that the first component has a concentration from about 2 to about 20 mg and the second component has a

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concentration from about 0.8% to about 15% of the first component. However, the concentration of the components does not make the claims patentable over the Bartlett et al patent since it is recognized in the art that synergism may be expected or unexpected (Synergism exhibited by a physical mixture of ingredients is a factor to be considered in determining the obviousness of the composition but it is not controlling since synergism may be expected or unexpected. *In re Hullmantel*, (CCPA 1963) 324 F2d 998, 139 USPQ 496; *Ethyl Corp. v. Ladd. Comr. Pats.* (DCDC 1963) 221 F Supp 751, 138 USPQ 663). The utility of the pharmaceutical compositions of the Bartlett et al patent to treat autoimmune diseases encompasses the method of instant Claims 20-26. See column 1, line 65 to column 2, line 6 of the Bartlett et al patent wherein it is disclosed that autoimmune disease includes systemic lupus erythematosus which is not specific to any organ. Bartlett et al discloses that the external manifestations of systemic lupus erythematosus are lesions on the facial skin. Bartlett et al discloses that in most cases, other areas of the skin and the mucosa are affected. Bartlett et al further discloses that nephritis, endocarditis, hemolytic anemia, leukopenia and involvement of the central nervous system are also observed. *In re Vaeck*, 947 F2d 488, 492, 20 USPQ 2d 1438, 1441 (Fed. Cir. 1991), states that for an invention to be obvious, two things must be found in the prior art: (1) the suggestion of the invention, and (2) the expectation of its success. In the instant case, both 1 and 2 are satisfied by the combination of the teachings of the Bartlett et al patent and the pertinent case law. Accordingly, it would have been obvious to one of ordinary skill in the art at the time of Appellants invention having the Bartlett et al patent before him to obtain the instantly claimed invention in view of the analogous structures of the compounds disclosed in the compositions used for the treatments and the resulting expectation of similar therapeutic properties.

Claim 29 is rejected under 35 U.S.C. 103(a) as being unpatentable over Bartlett et al (US Patent No. 4,965,276).

Appellants claim a process for the preparation of a pharmaceutical composition of Claim 12, which comprises processing a first component comprising 5-methyl-4"-

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trifluoromethyl-4-isoxazolecarboxanilide; a second component comprising the compound of the formula I, which is disclosed in Claim 12, or a stereoisomeric form of the compound of formula I, or a physiologically tolerated salt of the compound of formula I; and a third component comprising a pharmaceutically tolerated excipient, into a pharmaceutically acceptable form for administration.

The Bartlett et al patent discloses a pharmaceutical composition for use in the treatment of chronic Graft-versus-host diseases and autoimmune diseases such as systemic lupus erythematosus containing as the active ingredient at least one compound of the formula 1 or 2, compound 2 being present per se or in the form of a physiologically tolerable salt. The compound of formula 1 of the Bartlett et al patent embraces the first component of the composition of the instant claims because the first component having the name 5-methyl-4"-trifluoromethyl-4-isoxazolecarboxanilide represents the compound of formula 1 of the Bartlett et al patent. The compound of formula 2 of the Bartlett et al patent is analogous to formula I of the second component in the instant claims. See column 6, 2nd paragraph where Bartlett et al discloses that compounds 1 and 2 can be administered either alone or mixed with customary physiologically tolerated excipients, which embraces the third component indicated in instant Claim 12. The composition of the instant claims may differ from the compositions disclosed in the Bartlett et al patent by disclosing the first and second components together as one composition. It is not clearly stated in the Bartlett et al patent that compounds 1 and 2 have been combined together to form a composition. However, it is noted that the utility for the composition comprising compound formula 1 and 2 of the Bartlett et al patent are the same, that is, both compounds are used to treat chronic graft-versus-host diseases and autoimmune diseases such as systemic lupus erythematosus. *In re Kerkhoven*, 626 F2d 846, 205 USPQ 1069 (CCPA 1980), states that it is obvious to combine individual compositions taught to have the same utility to form a new composition for the very same purpose, which is what Appellants have done. The composition of the instant claims further disclose that the first component has a concentration from about 2 to about 20 mg and the second component has a concentration from about 0.8% to about 15% of the first component. However, the

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concentration of the components does not make the claims patentable over the Bartlett et al patent since it is recognized that synergism may be expected or unexpected (Synergism exhibited by a physical mixture of ingredients is a factor to be considered in determining the obviousness of the composition but it is not controlling since synergism may be expected or unexpected. *In re Hullmantel*, (CCPA 1963) 324 F2d 998, 139 USPQ 496; *Ethyl Corp. v. Ladd. Comr. Pats.* (DCDC 1963) 221 F Supp 751, 138 USPQ 663). Also, see column 6, lines 39-43, where Bartlett et al discloses that the compositions can be prepared for oral and rectal administration, which embraces instant Claim 29. *In re Vaeck*, 947 F2d 488, 492, 20 USPQ 2d 1438, 1441 (Fed. Cir. 1991), states that for an invention to be obvious, two things must be found in the prior art: (1) the suggestion of the invention, and (2) the expectation of its success. In the instant case, both 1 and 2 are satisfied by the combination of the teachings of the Bartlett et al patent and the pertinent case law. Accordingly, it would have been obvious to one of ordinary skill in the art at the time of Appellants invention having the Bartlett et al patent before him to obtain the instantly claimed invention in view of the analogous structures of the compounds disclosed in the compositions and the resulting expectation of similar therapeutic properties.

(11) Response to Argument

Applicants request correction of clerical errors in the Office action mailed April 17, 2002. The statement reciting that Claims 12-17, 20-26, and 29 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Bartlett et al (US Patent No. 4,965,276) for the reasons of record on page 2 of the Office Action mailed December 6, 1999 should have indicated that Claims 12, 15-17, 20-26 and 29 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Bartlett et al (US Patent No. 4,965,276) for the reasons already of record in the previously filed Office Actions. Appellants are correct in that no obviousness rejection was provided on page 2 of the Office Action mailed December 6, 1999. Appellants further note that Claim 29 was not rejected under 35 U.S.C. 103(a) in the Office Action mailed December 6, 1999 and therefore request the

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status of Claim 29. However, Claim 29 was rejected under 35 U.S.C. 103(a) as being unpatentable over Bartlett et al (US Patent No. 4,965,276) in the Office Actions mailed June 5, 2000, June 11, 2001 subsequent to a request for a continued prosecution application under 37 CFR 1.53(d) filed April 2, 2001, and April 17, 2002 subsequent to a request for continued examination under 37 CFR 1.114 filed March 12, 2002.

Appellants are correct in that Claims 13 and 14 are no longer pending.

Appellant's arguments filed July 17, 2002 in the Appeal Brief have been fully considered but they are not persuasive. On pages 7 and 8, under Section A of Appellant's Appeal Brief, Appellants argue that the prior art does not teach all of the elements of the claimed compositions and thus fails to establish a prima facie case of obviousness. More specifically, Appellants argue that the present claims are directed to combinations of compounds 1 and 2, wherein compound 2 is present at a concentration of about 0.8% to about 15% of the concentration of compound 1, which Appellants indicate would result in a maximum concentration of compound 2 to be about 3 mg since the instant claims only disclose compound 1 to be present at a maximum concentration of 20 mg. Appellants contend that in the description of the Bartlett et al patent, the lowest possible concentration of compound 2 is 10 mg. This argument is not persuasive since Appellants argument of the limitation of compound 2 to only 10 mg is based on compound 2 being in a dosage unit without the presence of compound 1 as part of the composition. The foundation of the rejection of the claims over the Bartlett et al patent is based on a composition comprising both compound 1 and 2 in the composition as suggested in the Bartlett et al patent.

On pages 8 to 14, under Section B of the Arguments presented in Appellant's Appeal Brief, Appellants argue that there is no motivation to modify the prior art to derive the claimed invention and thus fails to establish a prima facie case of obviousness. In response to applicant's argument that there is no suggestion to modify the reference, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in

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the art. See *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988) and *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, it is noted that the utility for the composition comprising compound formula 1 and 2 of the Bartlett et al patent are the same, that is, both compounds are used to treat chronic graft-versus-host diseases and autoimmune diseases such as systemic lupus erythematosus. *In re Kerkhoven*, 626 F.2d 846, 205 USPQ 1069 (CCPA 1980) states that it is obvious to combine individual compositions taught to have the same utility to form a new composition for the very same purpose, which is what Appellants have done. Thus, the motivation to modify the Bartlett et al patent has been established. Also, since the compounds of formula 1 and 2 of the Bartlett et al patent are analogous to the compound of the first component and the compound of the second component of formula I of the instant claims, one would be motivated to make modifications to obtain the instantly claimed inventions since the utility for the invention of the instant application is analogous to the utility indicated in the Bartlett et al patent.

Under Section B of Appellant's Appeal Brief, Appellants further present arguments with regard to the concentration of compounds 1 and 2 that is disclosed in the Bartlett et al patent, to show a lack of motivation to modify the Bartlett et al patent to derive the claimed invention. See the arguments presented on page 10 and 11 of Appellants Appeal Brief, which basically set forth that the Bartlett et al patent teaches higher concentrations of compounds 1 and 2 being necessary to achieve a desired biological effect. However, these arguments are not persuasive since the concentration for compounds 1 and 2 that is presented in the Bartlett et al patent are based on compounds 1 and 2 in separate compositions. In view of the common utility for compounds 1 and 2 in the Bartlett et al patent and the case law discussed above (*In re Kerkhoven*), one of ordinary skill in this art would be motivated to make a rejection of the claims based on a solid composition comprising both compounds 1 and 2 of the Bartlett et al patent together as one composition. In view of this position by the Examiner, Appellants may argue that the examiner's conclusion of obviousness is based upon improper hindsight reasoning. However, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon

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hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

Under Section C of the Arguments presented in Appellant's Appeal Brief, Appellants argue that a prima facie case of obviousness can be rebutted if Appellants (1) can establish "the existence of unexpected properties in the range claimed" or (2) can show "that the art in any material respect teaches away" from the claimed invention and further indicate that both are established by the evidence of record in the present case. However, the evidence that Appellants are referring to is not clear from this statement. The evidence of record as set forth in the Bartlett et al patent with regard to the establishment of compounds that are analogous to the compounds of the instant claims, the use of these compounds to treat diseases that are analogous to the diseases indicated as being treated in the instant claims, and the courts decision in *In re Kerkhoven*, 626 F2d 846, 205 USPQ 1069 (CCPA 1980), which states that it is obvious to combine individual compositions taught to have the same utility to form a new composition for the very same purpose, indicates Appellants have clearly fail to rebutt the examiner's prima facie case of obviousness.

Under Section D of the Arguments presented in Appellant's Appeal Brief, Appellants argue that the Bartlett et al patent teaches away from the claims since "a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." To support this point, Appellants argue that the higher concentrations disclosed for compound 1 and compound 2 in the Bartlett et al patent is evidence that Bartlett et al teaches away from the presently claimed invention. However, this argument is not persuasive because the concentrations presented for compounds 1 and 2 in the Bartlett et al patent are based on compositions comprising only compound 1 or compound 2 in the composition, not a composition comprising both compounds 1 and 2 in a solid composition together. The rejection of the claims before

the board establishes that compounds 1 and 2 in the Bartlett et al patent have common utility. The Examiner also point out that Synergism exhibited by a physical mixture of ingredients is a factor to be considered in determining the obviousness of the composition, but it is not controlling since synergism may be expected or unexpected. *In re Hullmantel*, (CCPA 1963) 324 F2d 998, 139 USPQ 496; *Ethyl Corp. v. Ladd. Comr. Pats.* (DCDC 1963) 221 F Supp 751, 138 USPQ 663. The evidence presented above shows that the Bartlett et al patent does not teaches away from the claimed invention and Appellants fail to rebutt any prima facie case of obviousness.

Under Section E of the Arguments presented in Appellant's Appeal Brief, Appellants contend that any prima facie case of obviousness would be rebutted by evidence of unexpected results. Appellants point to Table 1, at page 8 of the instant specification, which Appellants argue that the information disclosed therein shows a synergism of action between compound 1 and compound 2. However, the Examiner points out that synergism exhibited by a physical mixture of ingredients is a factor to be considered in determining the obviousness of the composition, but it is not controlling since synergism may be expected or unexpected. *In re Hullmantel*, (CCPA 1963) 324 F2d 998, 139 USPQ 496; *Ethyl Corp. v. Ladd. Comr. Pats.* (DCDC 1963) 221 F Supp 751, 138 USPQ 663. The Examiner also points out that "the fact that a claimed composition is more effective than anticipated is not persuasive of unobviousness where what is claimed would flow naturally from the teachings of the prior art. *In re Adams et al.* (CCPA 1960) 284 F2d 525, 128 USPQ 116; *In re Libby* (CCPA 1958) 255 F2d 412, 118 USPQ 94; *In re Crockett et al.* (CCPA 1960) 279 Fed 274, 126 USPQ 186; *In re Lieser* (CCPA 1947) 162 Fed 224, 74 USPQ 104; *In re Olsen* (CCPA 1944) 146 F2d 501, 64 USPQ 180.

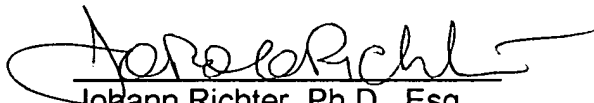
For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,



James O. Wilson
Supervisory Primary Examiner
Technology Center 1600
December 16, 2002

Conferees



Johann Richter, Ph.D., Esq.
Supervisory Primary Examiner
Technology Center 1600



Brain Davis, Ph.D.
Primary Examiner
Technology Center 1600

FINNEGAN HENDERSON FARABOW
GARRETT & DUNNER
FRANKLIN SQUARE BLDG SUITE 700
1300 I STREET N W
WASHINGTON, DC 20005-3315